pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Trastuzumab Emtansine (Kadcyla) for metastatic Breast Cancer

January 10, 2014

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): Kadcyla (trastuzumab emtansine)

Role in Review (Submitter and/or Manufacturer): Submitter/Manufacturer

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees X agrees in part ____ disagree

Hoffmann-La Roche fully supports the clinical criteria supporting the use of Kadcyla (trastuzumab emtansine) as outlined by the pERC. We would like to highlight that "pERC considered the magnitude of the benefit to be very meaningful and also noted that observing an improvement in overall survival in the second line metastatic setting is an unusual and important outcome." Additionally, "Patient advocacy group input indicated that patients with HER2 positive unresectable locally advanced or metastatic breast cancer valued extending life and prolonging progression-free survival. Therefore, based on the improvement in overall survival and progression-free survival demonstrated in the EMILIA study, pERC considered that T-DM1 aligned with these patient values."

Roche considered supporting the conversion of the initial recommendation to a final recommendation in order to ensure that patients can get access to Kadcyla (trastuzumab emtansine) as quickly as possible. However, we believe that a significant amount of information submitted by Roche was overlooked and as such, the value of Kadcyla (trastuzumab emtansine) is underestimated. We are concerned this will affect funding at the provincial level which could then delay patient access to Kadcyla (trastuzumab emtansine).

Clarification Required - Potential Next Steps:

"At the time of implementing a funding recommendation for T-DM1, jurisdictions may consider addressing the short-term, time-limited need for T-DM1 for patients who have already received lapatinib or capecitabine in the metastatic setting."

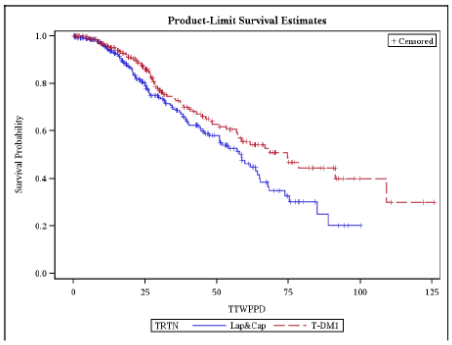
Clarification from pERC Requested: As a portion of 2nd line patients in Canada currently receive trastuzumab, please consider the short-term need for patients who previously received 2 lines of trastuzumab therapy.

Economic Issue #1 - Post Progression Survival

"As it is not possible to modify survival due to structural limitations of the model, there is a strong possibility that up to 50% of the benefit of trastuzumab emtansine can be attributed to the post-progression state due to extrapolation." "Further, the submitter also assumes that a patient's risk of dying would be improved with trastuzumab emtansine even though treatment would have been stopped."

Based on several questions from the economic reviewers during the review process, Roche provided substantial information on the post-progression survival benefit of Kadcyla (trastuzumab emtansine).

However, this information was not included in the economic reviewer reports, and as such, we are providing this information again for pERC to review as part of their reconsideration. Roche conducted a post-hoc analysis of post-progression survival based on a request from pCODR.



As depicted in the chart above, there was a clear separation of the survival curves which led to a statistically significant improvement (HR=0.71; 95% CI, 0.52-0.98; p-value 0.0351) in post-progression survival in the Kadcyla (trastuzumab emtansine) arm compared to the lapatinib and capecitabine arm for patients who had progressed under study treatment. The mean time from *progression to death* was 70 weeks in the Kadcyla (trastuzumab emtansine) arm compared to 55 weeks in the lapatinib and capecitabine arm, resulting in *an average of 15 additional weeks (.288 years) of post-progression survival for T-DM1*. Therefore the data shows a significant post-progression survival benefit and was not simply an "assumption."

Additionally, patients in both arms received similar anti-cancer treatments and anti-HER2 therapies and therefore, there was no bias towards Kadcyla (trastuzumab emtansine). Also note that the post progression HR (0.71) is very similar to the pre-progression HR (0.68) and as such, it would make sense to assume a similar risk reduction of death, both pre and post progression in our economic model.

Given the significant post progression survival, the reported ICERS would not be a "minimum", but a maximum.

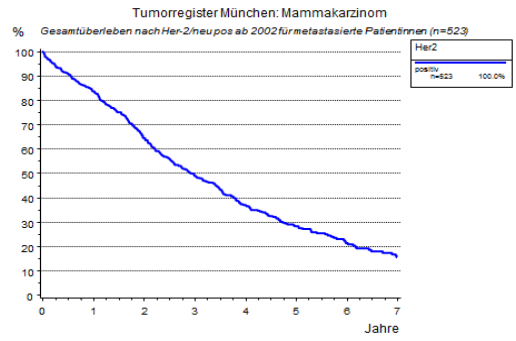
Question for pERC: Based on the information provided above, does Kadcyla (trastuzumab emtansine) provide significant post-progression survival? If so, please do not include inferences that the ICER is a "minimum" or "the true ICER might be double that of the EGP's lowest estimate."

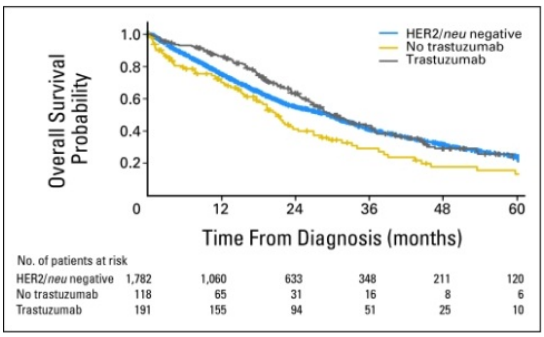
<u>Economic Issue #2 – Time Horizon</u>

"The pCODR CGP supported the Economic Guidance Panel assumed a time horizon of 5 years for a more conservative estimate."

CADTH's Guidelines for the Economic Evaluation of Health Technologies (third edition) "recommends using the time horizon for the natural course of the condition and the likely impact that the intervention will have on it." As provided within our submission, the time horizon was based on OS information from the "Tumorregister München" and the "registHER" registries (figures below). Both registries confirm that at 5 years after being diagnosed with HER2+ mBC, approximately 30% of HER2-positive MBC patients were still alive, while the Tumorregister further confirms that at 7 years from diagnosis more than 15% were still alive. Given that the average patient will progress on first line therapy after 12 months, 20% of patients would still be alive after 5 years of starting second line therapy and similarly 15% would be alive after 6 years.

Overall Survival KM Curves from the Tumorregister München and registHER





As well, when using a time horizon of only 5 years, the mean extrapolated post-progression survival gained in the model (using the EGP model extrapolation assumptions) *is only 0.213 years. This is less than the actual un-extrapolated post-progression survival gained in the trial (0.288 years).*

Lastly, in the August 2013 final pCODR recommendation for pertuzumab + trastuzumab, all pCODR reviewers agreed that 10 years was an appropriate time frame in the 1st line HER2+ metastatic setting. Given that Kadcyla (trastuzumab emtansine) treatment will begin 12 months after starting 1st line treatment (on average), an appropriate time frame would be 9 years.

Question for pERC: Based on CADTH guidelines, registry data, post progression data from EMILIA, and past precedence, why would 7-9 years not be considered an appropriate time frame for Kadcyla (trastuzumab emtansine)? If it is considered appropriate, the ranges of ICERs would be $126K-145K/QALY for the direct comparison and $82K-91K/QALY for the indirect comparison. Note that these ranges of ICERs already include wastage and extrapolation changes as per the EGP changes to the model.

Point for Clarification - Indirect Treatment Comparison

"pERC also discussed the cost-effectiveness of T-DM1 in comparison to trastuzumab plus capecitabine.....pERC further noted that although it was reasonable to have conducted the indirect comparison to trastuzumab plus capecitabine a better comparison in the Canadian context would have been to trastuzumab plus vinorelbine or other chemotherapies." "There was considerable uncertainty in the clinical estimates from the indirect comparison and the manufacturer did not provide any sensitivity analyses around these estimates."

There are currently no head to head trials for Kadcyla (trastuzumab emtansine) and trastuzumab + capecitabine in this setting. Roche provided an ITC as per Canadian CADTH Guidelines for Indirect Treatment Comparisons in Meta-Analysis. This was based on a systematic literature review and indirect comparison (200+ pages) that showed a statistically significant OS advantage for Kadcyla (trastuzumab emtansine) vs. trastuzumab + capecitabine. We will summarize some points to address the specific issues raised, but additional information can be found in the report:

Although trastuzumab plus vinorelbine may be considered another appropriate comparator, there are no Phase 3 trials of trastuzumab plus vinorelbine in patients who were previously treated with trastuzumab and a taxane in the metastatic setting. As such, this is not the same population eligible for Kadcyla (trastuzumab emtansine) and therefore, it is not appropriate to include trastuzumab plus vinorelbine in the ITC.

The methodology in the indirect comparison was deemed to be appropriate by the CGP. The CGP noted that "the most significant limitation in this indirect comparison is the quality of the trials included." However, these are the *only* other published phase 3 studies of HER2 targeted therapies in this setting. As well, both the GBG26 and EGF10051 were previously reviewed by JODR which ultimately led to the funding of lapatanib and trastuzumab in this setting in almost every province. As such, these are the only and best available evidence

for an ITC with Kadcyla (trastuzumab emtansine) in this setting.

Additionally, we repeated the ITC using Bayesian methodology as a sensitivity analysis, and found similar results to the main analysis. The main analysis resulted in significant HR's of 0.53 (PFS) and 0.56 (OS) while the sensitivity analysis resulted in significant HR's of 0.55 (PFS) and 0.58 (OS).

Question to pERC: Given that the ITC methodology was correct, sensitivity analysis confirmed the results and it was based on the only and best available evidence for Kadcyla (trastuzumab emtansine) vs. trastuzumab + capecitabine, please re-consider the appropriateness of the ITC and indirect cost-effectiveness analysis.

Conclusion: In summary, we believe that the stated ICERs of a minimum $162K/QALY and $98K/QALY were based on incomplete information. Even when using more conservative assumption of wastage and model extrapolation, the best and most appropriate ICER ranges are $126K-145K/QALY for the direct comparison and $82K-91K/QALY for the indirect comparison.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.

X Do not support conversion to final recommendation.
Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

1 Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer

of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.